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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,529	06/14/2005	Masahiro Toda	38102-76017	2773

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BARNES & THORNBURG LLP
11 SOUTH MERIDIAN
INDIANAPOLIS, IN 46204

EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,529	TODA ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,10 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8, 10, and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 04/30/2008 have been entered in full. Claims 5-7, 9, 11-15, 17, and 18 are cancelled. Claims 1-4, 8, 10, and 16 are under examination.

2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.

3. Applicant's submission, filed 05/06/2008, requesting a corrected filing receipt is acknowledged. Applicant's request was first made on 07/28/2005. The Examiner apologizes for the fact that this matter has not been addressed in any subsequent communication from the Office. The basis for Applicant's request is that the title on the filing receipt is the title translated from Japanese that appeared on the WIPO publication of the parental PCT application, and not the title that was submitted in the preliminary amendment on 06/14/2005 in this national stage entry. The filing receipt indicates that an application meets the minimum requirements to receive a filing date. The title of an application, like other parts of the specification, may be amended at any time during prosecution. Amendments to the title do not necessitate issuance of a corrected filing receipt, nor does the presence on a filing receipt of a title that does not match the title that ultimately appears on an issued patent in any way diminish the validity of the filing receipt. Applicants may be assured that the amended title has been entered into the record, and it will appear on any patent that may issue from this application. A signed Bibliographic Data Sheet bearing the correct title will be visible to Applicants in PAIR as of the entry of this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites "co-culturing the neural stem cell/neural precursor", but does not recite another cell or tissue to place in culture together with the recited neural cell. The recitation of "in the presence of granulocyte-macrophage colony stimulating factor" does not define a co-culture.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 8, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing proliferation of an endogenous neural stem cell/neural precursor, comprising contacting said endogenous cell with a locally administered composition consisting essentially of GM-CSF, does not reasonably provide enablement for a method for inducing proliferation of an endogenous neural stem cell/neural precursor, wherein GM-CSF is administered distally or wherein GM-CSF is the sole agent contacted with neural stem cell/neural precursor cells in vitro in the absence of an additional cell type. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

8. The prior art is silent as to direct effects of GM-CSF or the presence of GM-CSF receptors on neural stem cells/neural precursors. The instant specification establishes an effect of GM-CSF on endogenous neural stem cells/neural precursors when the factor is applied locally to its site of desired action in vivo. Endogenous neural stem cells/precursors are significantly increased by local administration of GM-CSF to the injured site of the spinal cord (Examples 7 and 9); the same treatment also causes dendritic cells to be induced in the spinal cord (Example 8). Administration of GM-CSF directly into the carotid artery significantly improved neurological properties obtained immediately after cerebral infarction (Example 10).

9. The disclosed evidence indicates that GM-CSF exerts its effects on neural stem cells/neural precursors by acting upon dendritic cells, or other cells, which in turn secrete neurotrophic substances. The specification teaches that dendritic cells, when co-cultured with neural stem cells in vitro, cause the neural cells to markedly proliferate (Example 5); experiments involving transfer of cell culture media confirmed that a secreted factor of dendritic cells causes neural stem cells to proliferate (Example 6). As noted, the increase in endogenous neural stem cells/ neural precursors that occurs after administration of GM-CSF to the spinal cord coincides with an increase in dendritic cells (Examples 7-9). The instant specification suggests, that the CNS effects of GM-CSF observed in Example 10, may be due to activation of microglia (FIG. 22). The specification does not show that GM-CSF can act as a sole agent to promote proliferation of neural stem cells, as required by instant claim 2, for example. As the active factor apparently is produced locally, it is not clear that distal administration of GM-CSF

would cause sufficient production of the required factors at any particular site where stimulation of proliferation of neural stem cells/precursors is desired in vivo. The instant specification exemplifies only administration to an injury site in the spinal cord or into the carotid artery directly upstream of a site of induced infarction.

10. It is not clear that a method of stimulating proliferation of neural stem cells/precursors, wherein GM-CSF can act as the sole essential agent in the absence of cells other than neural stem cells/neural precursors would ever by achieved regardless of how much experimentation a skilled artisan might be willing to perform.

11. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. Claim 16 is drawn to a method of treatment wherein neural stem cells/neural precursors are first induced to proliferate in vitro in the presence of GM-CSF and then administered to a patient with any nerve injury or nerve function insufficiency. As noted above, the instant specification does not establish that the first part of this claimed method, wherein GM-CSF is required to act as a sole agent to stimulate proliferation of neural stem cells/neural precursors, is even possible. Furthermore, even if the first step were accomplished, the instant claim broadly encompasses administering the proliferated cells for the treatment of all diseases of the nervous system. The method of claim 16 is not limited to any particular disease. The specification does

not provide any examples in which cells were produced by a claimed method and further does not provide any examples cells thusly produced were tested for treating any disease. The instant specification provides no guidance or example to provide enablement for even a single embodiment of the claimed method. Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991).

13. The state of the art does not provide enabling guidance that is lacking in the instant specification with regard to stem cell therapies for diseases or injuries to the nervous system. The claimed methods encompass treatment of diseases that the currently lack effective treatments, such as brain tumors and neurodegenerative diseases. Reviews published after priority date of the instant application indicate that this is a highly complex art and that results are unpredictable. Lindvall et al., *Nature Medicine* 10, S42-S50 (2004), for example, point out that, in each disease, a different spectrum of cell types is affected (Lindvall et al., page S42, left column). Regarding Parkinson's disease, for example, "it remains to be shown that the stem cell-derived neurons, after implantation in animal models, fulfill the requirements of successful graft-that is, to reinnervate most of the of the denervated striatum, restore dopamine release in vivo and substantially improve Parkinson's-like symptoms" (Lindvall et al., page S43, left column). Bone marrow-derived cells were also described to give rise to neurons in the stroke-damaged brain, but these cells were not pre-differentiated in vitro and it is controversial whether donor cells differentiated into neurons or fused with endogenous neural cells (Lindvall et al., page 546, left column). For ALS, recent findings support the "strategy of differentiating stem cells along specific cortical neuronal lineages *in vitro* and transplanting them so as to reconstruct cortical circuitry" (Lindvall et al., page 548, left column). Specific lineages are not described in the

instant specification. Further, "it is unknown, though, if such cortical neuronal replacement will work in the brains of individuals with ALS" (Lindvall et al., page 548, left column).

14. Therefore, the instant specification asserts, but does not enable, a novel method of producing cells that may ultimately prove to be useful for cell therapy of neural disease, and then does not provide enablement for cell therapies beyond that which was known in the art at the time of filing. The courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997).

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claim 8 is rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6946548, filed September 10, 2001. The '548 patent teaches kits comprising GM-CSF and a medium comprising a growth factor at column 6, lines 51-57. Such a kit is indistinguishable from the kit of instant claim 8, regardless of any expression of intended use.

Conclusion

17. No claims are allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647

/David S Romeo/
Primary Examiner, Art Unit 1647